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09/980,526	04/01/2002	Mark J Federspiel	07039-278001	5918

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

KD

Office Action Summary	Application No.	Applicant(s)	
	09/980,526	FEDERSPIEL, MARK J	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-63* is/are pending in the application.

4a) Of the above claim(s) *47,50,56 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46,48,49,51-55,57,58 and 60-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20020903*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The preliminary amendments filed 11/15/01 have been entered, with the effect that original claims 1-39 and added claims 40-45 have been cancelled; and new claims 46-63 have been added. With respect to the newly added claims, Applicant's response fails to indicate where and how the claims are supported by the original disclosure, as is Applicant's burden. See MPEP 714.02, last sentence of the third paragraph from the end and 2163.06 (I), last sentence.

Election/Restrictions

Claims 47, 50, 56 and 59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the response filed 8/7/03.

Applicant indicates that claims 50 and 59 are readable on the elected species, a fusion of PERV-gag and RNase H. However, the specification does not characterize gag as being a "surface glycoprotein." The only mention of a "surface glycoprotein" that the Examiner could find in the specification referred specifically to the ORFS/pre-S protein of herpesviruses (p. 4, line 33). The specification also mentions "viral glycoprotein" in the context of receptor interference (page 5, lines 12-14). However, such embodiments do not embrace the elected species. Consequently, claims 50 and 59 have been withdrawn from consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on International application WO 00/14296 filed on 5/24/00. It is noted, however, that applicant has not filed a

certified copy of the International application as required by 35 U.S.C. 119(b). Furthermore, since the instant application was filed under 35 USC 371 as the national stage of the International application, the International application is not a prior application, i.e. it would be *unnecessary* to perfect the foreign priority claim by providing the certified copy.

Drawings

New corrected drawings are required in this application because of the objections by the draftsperson set forth on the attached PTO-PTO-948, and no detail can be seen in Figures 4 and 10. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46, 48, 49, 51-55, 57, 58, and 60-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

None of the claims place any limitation on the role or function of the nucleic acid molecule in the context of the claimed method. Claims 46, 53-55, 62, and 63 do not require the nucleic acid molecule to be linked to a promoter, nor that it be expressed. It is clear from the specification e.g. page 4, that the nucleic acid molecule is expressed, which requires a promoter, and that the product expressed from the nucleic acid is what mediates the reduced transmission of the infectious agent. The only product described as being expressed is a polypeptide, e.g. a soluble receptor or a fusion protein comprising a viral protein and degradative enzyme. Applicant has failed to indicate where the original disclosure supports the invention as it is now being broadly claimed.

Claims 46, 48, 49, 51-55, 57, 58, and 60-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a broad method of reducing transmission of an infectious agent following transplantation of cells, tissue or organs in a mammalian transplant recipient, either

from the donor cells to the recipient or from the recipient to the donor cells. The claims are not limited with respect to the infectious agent, which includes viruses, bacteria, and parasites (specification, p. 4). However, the specification provides no guidance whatsoever on how to practice the claimed invention where the infectious agent is a bacterium, parasite, or any other non-viral infectious agent. There is no evidence of record of prior art that would serve to supply any guidance as to how one would practice the claimed invention with respect to non-viral infectious agents. As will be discussed in more detail below, the guidance on practicing the invention to reduce transmission of viral infectious agents is greatly limited. Consequently, the specification fails to provide a disclosure adequate to enable one to make the donor cells required for, or otherwise practice, the invention as broadly as claimed with respect to the scope of infectious agent.

The claims broadly require only that the donor cells be modified by introduction of a nucleic acid molecule. The claims do not require that the nucleic acid molecule be any particular type of nucleic acid molecule, or play any role in reducing the transmission of the infectious agent, or that it be expressed in the donor cell (which as indicated above constitutes new matter). However, as disclosed in the specification, the nucleic acid is operably linked to a promoter and expresses a protein in the donor cells, wherein the protein is responsible for reducing the transmission of the infectious agent. While the claims embrace any means of reducing the transmission, the specification discloses only two classes of nucleic acid. The first class of nucleic acid molecule expresses, in the donor cell, a soluble receptor which binds either to a mammalian cell surface protein to which a viral infectious agent would bind, or binds to a viral surface protein which binds to a target mammalian cell. This general methodology is termed

"Receptor Interference" (RI) in the specification, and is described on pages 23-25. The aim of RI is to interfere with the binding of virions, produced in the recipient or in donor cells, to donor cells or recipient cells, respectively. The second class of nucleic acid molecule encodes a fusion protein comprising a viral protein, present in the virion of a viral infectious agent, and a degradative enzyme, e.g. a lipase, protease or nuclease. This general methodology is termed "Capsid-targeted Viral Inactivation" (CTVI) in the specification, and is described at pages 16-23. The aim of CTVI is to have virions of the infectious agent incorporate the fusion protein, and lead to inactivation of the virion by action of the degradative enzyme on virion components. While the claimed invention embraces these two classes of nucleic acid molecule, it also broadly embraces any nucleic acid which either directly or indirectly, by virtue of its expression product, would inhibit the transmission of a viral or non-viral infectious agent at any point in the life cycle of the infectious agent. The specification provides no guidance whatsoever on nucleic acid molecules required to practice the claimed invention which are not the means for an RI method or a CTVI method.

Applicant has elected the species where porcine endogenous retrovirus (PERV) is the infectious agent and the nucleic acid molecule encodes a fusion protein comprising the PERV gag protein (or part thereof) and RNase H. The elected species falls within CTVI methodology.

At the time the invention was made, experience with CTVI was limited to the investigative stage to determine whether it was a viable method to treat an ongoing viral infection. Boeke et al. (Trends Microbiol. 4 (11) : 421-426, Nov. 1996) reviews this strategy at the time the invention was made. Boeke discloses that three main technical difficulties must be overcome to practice this strategy. First, the fusion protein expressed from the nucleic acid

molecule must be capable of being assembled into virions, which is mediated by the viral protein moiety of the fusion protein. Second, the fusion protein must be packed in a manner that allows the toxic moiety, e.g. the degradative enzyme, of the fusion protein to degrade or inactivate the target viral component. Third, the toxic moiety must be controlled in some way that it is not toxic to the cells expressing the fusion protein. Boeke discloses that "[I]t is not obvious how to design fusion proteins that can deliver their toxic cargo into a virion whose three-dimensional structure is unknown" (page 421, col. 1). Boeke discloses that the method had practiced successfully in cultured cells only with Mo-MLV (a retrovirus) and the yeast TY1 retrotransposon. In the case of Mo-MLV, the only fusion proteins shown to have any effect whatsoever where fusions of gag and either staphylococcal nuclease (SN) or *E. coli* RNase H. Fusions of SN to the Ty Pol were packaged into Ty1 particles, but had no effect on transposition. A fusion of Ty Pol to a specific mutant barnase was highly toxic to yeast, however, some mutants were identified which when expressed in yeast under certain conditions could inhibit transposition without killing the yeast (page 422). However, Boeke does not disclose any information on these mutants other than their existence. The instant specification discloses that barnase could be used in the claimed invention, but fails to disclose any mutant barnase protein that could be used, i.e. that would not kill the donor cell. Boeke reports that a similar strategy had been applied to HIV, but no one had succeeded with a Gag-nuclease fusion (page 423, col. 1). In addition, Vpx-SN and Vpr-SN fusion proteins had been examined for targeting of HIV virions, but no evidence of significant anti-viral activity had been obtained. The reasons for lack of success were unclear, but appeared to be due to proteolytic degradation of the fusion protein, or that the location of the fusion proteins in the virion did not allow degradation of the viral

genomic RNA. Thus, even knowledge of the virion structure of HIV was not sufficient to allow design of a successful CTVI fusion protein for this lentivirus. Boeke discloses that CTVI was unknown for viruses other than retroviruses, it was unknown whether anti-viral proteins could be delivered to their virions, and that the virion structures and their protein components were only in the process of being determined (page 424).

With respect to the choice of degradative enzyme, the specification lists nucleases, proteases and lipases (protein kinases are also mentioned, but are not degradative enzymes). However, as disclosed by Boeke, choosing suitable nucleases was unpredictable, largely due to the unknown toxicity of the fusion protein to cells, and choosing suitable viral proteins to which the nuclease should be fused. There was no experience with other degradative enzymes, such as proteases, lipases, or with protein kinases. The instant claims embrace fusing the enzyme to any viral protein and embrace any enzyme. However, the specification provides no guidance as to which specific enzymes, other than SN and *E. coli* RNase H, would both be sufficiently low in toxicity and yet succeed in inactivating virions, and no guidance as to which specific viral proteins different specific enzymes could be attached. By simply stating that various other viral proteins and enzymes may be useful, the specification does no more than present an invitation to one of skill in the art to experiment and find out for themselves how to make and use the invention throughout its scope.

The instant specification (Example 1) presents experiments on inhibition of Mo-MLV infection or active virion production in cultured cells with gag fusions to SN or RNase H, similar to that reported in Boeke. The inventors concluded from these experiments that only a slight antiviral effect was attributable to the fusion protein in cells with established infection (page 30,

lines 4-6). The instant specification does not provide any new guidance on practicing the invention with retroviruses or on any other virus. At best, the specification provides specific guidance commensurate only with what was already known in the prior art regarding potentially useful fusion proteins and target viruses. The specification also fails to provide any working examples of the claimed invention for reducing transmission of a viral infectious agent for any virus, whether retrovirus in general, or PERV in particular.

In summary, Boeke illustrates that CTVI even for use in cultured cells was still largely hypothetical, and highly unpredictable at the time the instant invention was made, and what little success had been achieved in cultured cells, was limited to inhibiting Mo-MLV in cells expressing a fusion of MoMLV gag and SN or *E. coli* RNase H. With respect to application of CTVI *in vivo*, Boeke discloses that it was unknown "[W]hat efficiency of antiviral gene delivery, even for the perfect antiviral protein, is required to result in a therapeutic effect on viral infection *in vivo*" (page 424). The instant specification does not advance this field in any way, other than to suggest another potential use for the method.

While Boeke focused on delivering nucleic acid molecules to cells of a subject suffering a viral infection, the instant method, as disclosed in the specification, involves delivering the nucleic acid molecules to cells, tissues or organs *ex vivo* or by producing transgenic donor mammals whose genome contains the nucleic acid molecule. With respect to *ex vivo* delivery, the specification provides no guidance on how the nucleic acid molecules would be delivered to non-dividing cells, tissues or organs, and no guidance as to what fraction of the cells in the tissue or organ would be required to contain and express the nucleic acid molecule, or what level of expression would be required in order to reduce transmission of a viral infectious agent either

from donor cells to recipient, or from recipient to donor cells. The only working example relating to CTVI involved the use of a retroviral vector to deliver the nucleic acid molecule to dividing, cultured cells. However, retroviral vectors are not able to transfect non-dividing cells, such as the terminally differentiated cells of tissues and organs. The specification mentions that transgenic mammals could be made, but provides no guidance on how to actually make such transgenic mammals. While the fusion proteins described in the prior art were not toxic to cultured cells, one cannot predict the effects of expressing these fusion proteins during the development of a transgenic mammal.

The elected species is directed to reducing transmission of PERV from porcine cells. As disclosed in the specification, the aim of this embodiment is to reduce the transmission of PERV from porcine donor tissue to human recipients. As discussed in the specification, those in the xenotransplantation art , e.g. Weiss (Nature 391: 327-328, 1998), were concerned that PERV might be able to productively infect humans receiving transplanted porcine cells, tissues, or organs, in part because of findings that some cultured human cells could be infected by PERV. The instant specification (Example 2) shows such experimental evidence. However, at the time the invention was made is was unclear whether productive PERV infection would occur *in vivo* in xenotransplant recipients, see for example Patience et al. (Lancet 352: 699-701, 1998) and Heneine et al. (Lancet 352 : 695-699, 1998). While published well after the instant application was filed, Xu et al. (ASAIO J. 49 (4): 407-416, 2003 at page 407, col. 2) and Ritzhaupt et al. (J. Virol. 76 (22): 11312-11320, Nov. 2002, at page 11312-11313) summarize the results of studies on the transmission of PERV from porcine xenografts to various mammals, including human xenotransplant patients, from before the filing of the instant application. Evidence of PERV

transmission from porcine xenografts in SCID mice had been observed by some, but not all, investigators (Xu), but that the transmission was non-productive (Ritzhaupt). No evidence of transmission had been obtained for other small mammals, including rats, mink, and guinea pigs, making it unlikely that a small animal model for PERV xenozoonosis could be established (Xu). No evidence of transmission had been obtained for human or non-human primate recipients (Xu and Ritzhaupt). Both make clear that no animal model existed for examination of PERV transmission from porcine xenografts, and Ritzhaupt makes clear that an animal model is critical for understanding PERV infection and possible pathogenesis. The importance of this evidence is two-fold. In order for one to practice the elected method successfully, there must be a level of transmission of PERV to be reduced. If xenozoonotic transmission of PERV does not occur, then there is nothing to reduce and the method is inoperative. Secondly, even if xenozoonotic transmission of PERV would occur in some recipient mammals, the lack of any animal model of such transmission would prevent one of skill in the art from determining which of the broad scope of embodiments of the elected (and claimed) invention are operative and inoperative. Also, there is no evidence of record to indicate that animal models were available for xenozoonotic transmission of the broad range of other infectious agents embraced by the generic claims. Thus, in order for one to practice the invention throughout its broad scope, one would first have to develop such animal models to be able to assess whether any particular embodiment of the claims was operative.

A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Tossing out the germ of an idea does not constitute an enabling disclosure. While every aspect of a generic claim need not have been carried out by an inventor,

or exemplified in the specification, reasonable detail must be provided in order to enable the skilled artisan to understand and carry out the invention. It is true that a specification need not disclose what is well known in the art. However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. The rule that a specification need not disclose that which is well known in the art simply means that omission of minor details does not cause a specification to fail the enablement requirement, and is not a substitute for an enabling disclosure. However, if there is no disclosure of starting materials and of conditions under which the process can be carried out, undue experimentation is required. Failure to provide such teachings can not be rectified by asserting that the disclosure of the missing necessary information was well known in the prior art. See *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 101, 1005 (CA FC, 1997). In this case, the specification fails to provide either the starting materials or process conditions for practicing the elected invention for any embodiments other than for inhibiting transmission of retroviruses in cells expressing a fusion protein comprising the gag of the retrovirus and either staphylococcal nuclease or RNase H. It does not disclose starting materials or process conditions for practicing the invention for reducing transmission of other viruses, or *in vivo* to reduce transmission of a virus, including retrovirus, between donor cells and a recipient.

Thus, in view of the extreme breadth of the claims, particularly when coupled with the primitive state of the CTVI art, the unpredictability in this art, the lack of guidance provided by the specification beyond what was known in the art, the lack of any suitable model system for testing the efficacy of the invention, and the lack of any working example of the claimed

invention, it would clearly require undue experimentation to practice even the elected species, much less practice the invention as broadly as claimed.

Claims 46, 48, 49, 51, 52, 55, 57, 58, 60, and 61 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: transplanting the donor cell into the mammalian recipient. Claims 46 and 55 are directed to a method for reducing transmission of an infectious agent from recipient to donor cell or from donor cell to recipient. In order for such a method to be complete, transplantation of the donor cell into the recipient must be carried out, as recited in claims 53, 54, 62, and 63. Otherwise, the method makes no sense. This rejection would be overcome by the addition of a step of transplanting the donor cell into the mammalian recipient.

Double Patenting

Applicant is advised that should claims 53 and 62 be found allowable, claims 54 and 63, respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). It is noted that should claims 46 and 55 be amended in response to the rejection under 35 USC 112, ¶2 set forth below to add a transplantation step, claims 46 and 55 would also be duplicates of claims 53 and 62, respectively.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Scott D. Priebe
Primary Examiner
Art Unit 1632